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AGE AND BIOPSY AS PREDICTIVE FACTORS IN THE MANAGEMENT OF ORAL SQUAMOUS CELL CARCINOMA

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Abstract

Clinical observation has shown that the growth rate and regional metastasis of squamous cell carcinoma of the oral cavity is more aggressive in younger patients than in patients older than 60 years. Secondly, any surgical interference, such as incisional biopsy and/or incomplete surgical excision, has been shown to aggravate the clinical behavior of the tumor. Accordingly, the objective of this study was to examine the effect of patient age and incisional biopsy on outcomes.

This prospective study enrolled 35 patients with oral squamous cell carcinoma who were divided into 2 groups. Group I consisted of patients ≥ 60 years, whereas group II consisted of patients < 60 years. Clinical comparisons between these 2 groups were made. Patients in groups I and II were subjected to different treatment plans according to patient age and the presence or absence of neck metastasis.

Patients in-group II presented with a greater frequency of neck metastasis than patients in group I (56% vs. 18%; $p < 0.05$). Five years of follow-up after aggressive surgery revealed a survival rate of 67% in group II and 65% in group I ($p > 0.99$) after conservative surgery. In group I, there was a trend towards a greater percentage of patients with no initial evidence of neck metastasis developing neck metastasis after incisional biopsy compared with patients who did not undergo biopsy (80% vs. 22%, $p=0.09$).

In conclusion, age is considered a predictive factor in nodal metastasis of oral squamous cell carcinomas, and incisional biopsy aggravates the clinical behavior of the tumor.

Introduction

To establish any form of treatment for oral carcinomas, special consideration should be given to their metastases to regional lymph nodes. Radical neck dissection ensures the en block removal of all cervical lymph channels and nodes that drain the primary site.

Modified neck dissection has been described[1] as a means of saving one internal jugular vein as well as saving other structures which are unnecessary to be removed, especially in patients with a clinically negative neck. The decision of whether to perform an elective dissection in a patient with a clinically negative neck has occupied the minds of many surgeons. The main issue is the presence or absence of micrometastases in these patients.

Unfortunately, until now, there has been no method available that would actually improve the clinical staging of the neck. High-resolution computed tomography has been tried, but it was found to be of no advantage over physical examination[2]. In another study[3], positron emission tomography (PET) scanning using fluorodeoxyglucose (FDG) as a substrate was used. The authors concluded that FDG-PET does not contribute to the preoperative workup and that it does not replace supraomohyoid neck dissection as a staging procedure. Nahmias et al[4]

investigated the role of 18-fluorine FDG-PET/CT scanning in the preoperative prediction of the presence and extent of neck disease. They concluded that a negative test would not help the surgeon in the management of the patient with a clinically node-negative neck because of the rate of false-negative results.

David et al[5]. Used ultrasonography (US) – guided fine–needle aspiration with cytologic examination combined with lymphoscintigraphy for the identification of sentinel lymph nodes (SLNs). Patients with disease-free SLNs may be spared elective regional lymph node dissection. In addition to this procedure requiring a highly experienced radiographer, it has its limitations.

The overall incidence of neck nodes to be involved with metastases is high; therefore their removal ensures complete excision of the tumor and its draining lymph nodes[6].

Although the principal of performing a maximal operation for a minimal disease would be of great value to these patients from an oncological point of view, such radical surgery is unnecessary in patients with a clinically negative neck. Some surgeons perform radical neck dissection in any patient in whom the neck must be entered to eliminate the primary tumor[7]. Others perform radical neck dissection depending on the size, site, depth, and histological differentiation of the tumor. One advantage of this radical surgery is that it will be of value in the staging procedure, the result of which determines whether or not postoperative radiotherapy and chemotherapy are necessary. Supraomohyoid neck dissection is of comparable therapeutic value and provides the same staging information as classical dissection[8]. Still, other surgeons would find the attitude of wait-and-see beneficial. In this article, the decision of whether to perform neck dissection in a patient with a clinically negative neck was influenced by the age of the patient.

Patients and methods

Patient groups

This prospective study was conducted at the Department of Maxillofacial Surgery, Basrah General Hospital, Iraq from 1990 until 2000. The study involved 35 patients, all with squamous cell carcinoma of the oral cavity, who were divided into 2 groups according to their age. Group I consisted of 17 patients who were $\geq$ 60 years of age. Group II consisted of 18 patients who were < 60 years of age. Most of the patients (77%) presented late in their disease process.

Evidence of metastasis on presentation

In group I, 3 of 17 (18%) patients had clinical evidence of neck metastasis on presentation, whereas 10 of 18 (56%) patients in group II had evidence of neck metastasis on presentation ($p<0.05$) (Table 1). This significant difference between groups necessitated different treatments, which impacted other studied variables (e.g., survival rates).

Incisional biopsy

Incisional biopsy was avoided when possible, especially in those in group I who had no clinical evidence of neck metastasis; only 5 patients in group I underwent incisional biopsy. In group II, all of the patients underwent incisional biopsy except for those with a T1, tumor size who underwent excisional biopsy. Results from the histological examination of the biopsy specimens are shown in Table 1.

Operations

Group I: Patients without clinical evidence of neck metastasis underwent local resection (LR) of the primary tumor only, regardless of its size. Patients with clinical evidence of neck metastasis underwent LR of the primary tumor together with supraomohyoid (SOH) neck dissection (Fig. 1).

Group II: Patients without clinical evidence of neck metastasis underwent LR of the primary tumor if its size was 2 cm in diameter or less. If the tumor size

Table 1. Patient and tumor characteristics

Distribution		Group I	Group II
Age	Age	60-76	35-58
	Total No.	17	18
	Female	6	8
	Male	11	10
Site	Tongue	4	2
	Maxilla	3	5
	Floor of the mouth	6	8
	Lip	4	2
	Cheek	0	1
Tumor size T stage	T1	1	3
	T2	2	2
	T3	3	0
	T4	11	13
Involve. of lymph nodes	N0	14	8
	N1	1	1
	N2	1	4
	N3	1	5
Histopath. Different. of Primary Tumor	Well differ	10	15
	Mod. differ	4	2
	Poorly differ	3	1

was greater than 2 cm in diameter, then LR was combined with radical neck dissection (RND) (Fig. 2). Patients with clinical evidence of neck metastasis underwent LR and RND together with postoperative radiotherapy.

Statistical analysis

Chi-square or Fisher's exact test and contingency tables were used to establish statistical significance ($p < 0.05$). Statistical analysis was performed using GraphPad Software (La Jolla, CA).

Results

Group I: Fourteen patients without clinical evidence of neck metastasis underwent LR of the primary tumor only (Fig.1). One of those patients died of a recurrence at the primary site. Six patients developed neck metastasis. Four of these 6 patients underwent a secondary surgery (RND); 2 of those patients died of a recurrence at the neck 18 months after the initial surgery. One died of unrelated disease and the other survived. The remaining 2 of the 6 patients who developed neck metastasis refused secondary surgery and both died.

The 3 patients with clinical evidence of neck metastasis underwent LR with supraomohyoid neck dissection, and these patients successfully survived the procedure.

Group II: Eight patients without clinical evidence of neck metastasis, 3 of whom had a tumor size ≤ 2 cm in diameter, underwent LR only (Fig 2). Two of these patients developed neck metastasis; both underwent RND and radiotherapy and both survived. Five patients whose tumor size was > 2 cm in diameter underwent LR and RND. Only one patient developed a recurrence at the neck and died 2 years after the initial treatment. The remaining 4 patients survived. The 10 patients with clinical evidence of neck metastasis underwent LR, RND, and radiotherapy. Four patients experienced a recurrence at the neck; one patient experienced a recurrence at the primary site. All 5 of these patients died within 2 years after the initial surgery. The 5 remaining patients survived.

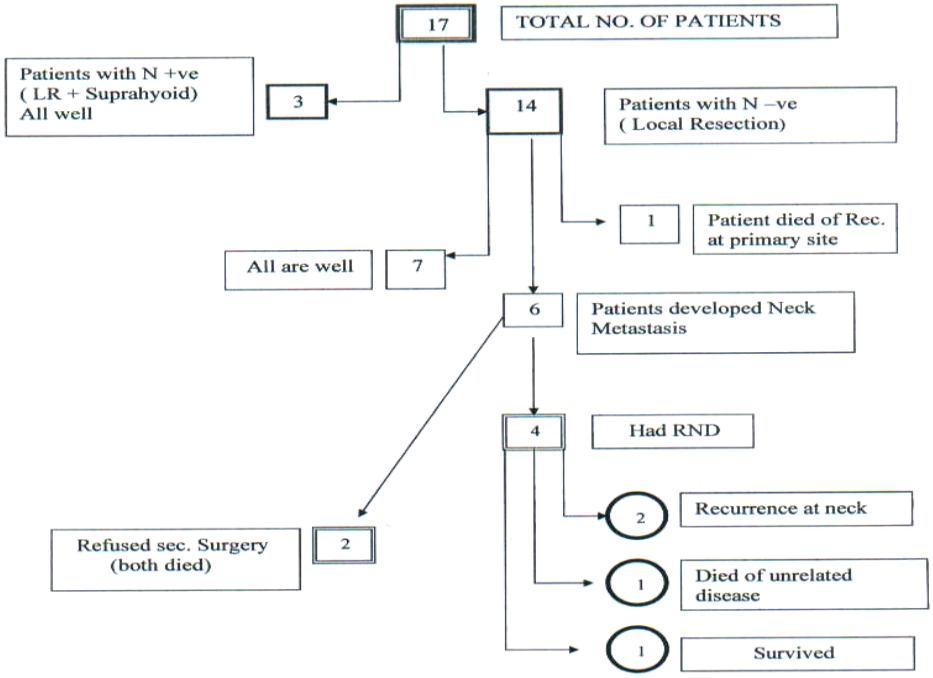
Five-year survival rates

Five years of follow-up revealed a survival rate of 12 of 18 (67%) patients in group II and 11 of 17 (65%) patients in group I. These 5-year survival rates did not significantly differ between groups ($p > 0.99$).

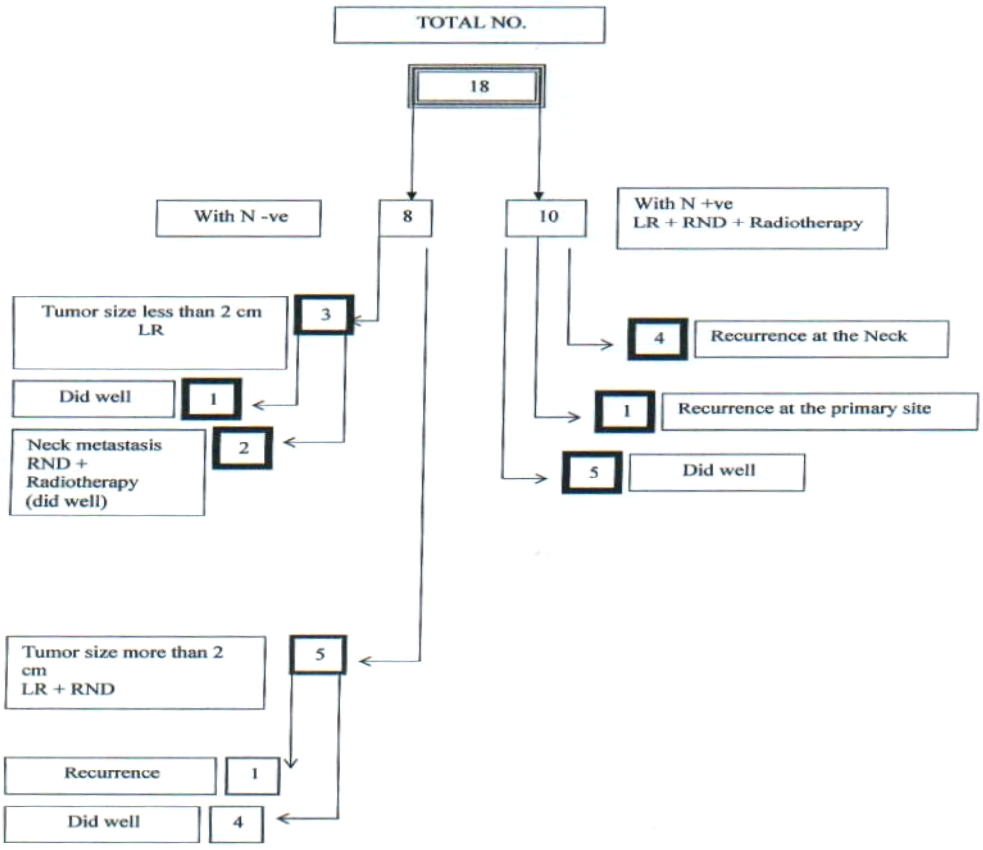
Influence of incisional biopsy on development of neck metastasis

In group I, 4 of the 5 (80%) patients who underwent incisional biopsy and who initially had no evidence of neck metastasis developed neck metastasis within 6 months after the surgery.

Group (I) Patients above 60 years of age



Group II
Patients below 60 years of age



In contrast, only 2 of the 9 (22%) patients who did not undergo biopsy and who initially had no evidence of neck metastasis developed neck metastasis. Although this difference in the rates of developing neck metastasis between groups did not reach statistical significant (p=0.09), there was a trend towards a greater incidence of developing neck metastasis among patients who underwent incisional biopsy.

In group II, although 8 patients had no evidence of neck metastasis at presentation, we suspected those patients of having micrometastases. Therefore, we performed RND except for in those 3 patients whose primary tumor size was < 2 cm in diameter. In those patients, we performed excisional biopsy; 2 of these 3 patients developed neck metastasis.

Discussion

It is a common surgical finding in our patients with squamous cell carcinoma of the oral cavity that, when a small piece of tumor tissue is taken during an incisional biopsy, the defect created is filled with regenerated tumor within a few days. Furthermore, the tumor size has increased appreciably. It is believed that this clinical finding is due to spillage of tumor cells at the operative site, with subsequent local dissemination of the tumor cells to new areas. Animal studies have shown a positive correlation between surgical trauma and an increase in tumor growth at both primary and metastatic tumor sites. This effect has been attributed to posttraumatic immune suppression. Humans who undergo surgery also sustain suppression of immune function that has been correlated with a poor outcome. Although there is evidence that postoperative immune suppression may result in enhanced tumor growth, this evidence remains inconclusive[9].

Based on certain facts, which will be discussed below, it may be that immune suppression is *not* the cause of enhanced tumor growth; in fact, the opposite may be true.

The fact that tumor cells escape the level of surveillance does not implicate the immunological system in any dysfunction. Once the tumor has formed, then the coordination between the specific and nonspecific immune system presents a real threat to tumor cells, at least in their early stages of development. Further growth of the tumor, which takes a slow spontaneous progression, will depend on host-tumor interactions. However, there is no evidence that this delay in tumor autonomy is due to any major immunological inhibitory influence. In fact in some systems, the opposite appears to be the case[10], i.e., low immunological vigor may slow tumor progression. This may explain the slow tumor growth rate in older patients, who have an appreciable loss of immunological vigor; this is characterized by a reduction in T-cell function and number as well as a decrease in the primary immune response of B cells, especially for those responses requiring T-cell interaction[11]. It is well known that there is a depression in most aspects of the cell-mediated immune response in patients with head and neck cancers[12]. There is a functional depression of NK activity[13], and for some tumors, although there is an increase in immune complexes in some patients with oral cancer[12], these may block the immune response[14].

The etiology of immune suppression in cancer patients remains obscure. However, it is possible that it may be the result of humoral factors elaborated by the cancer cells; it also may be the result of a complex physiological response of the body against the cancer cells, which can depress normal cell-mediated immunity[15]. If the latter is true, then immune suppression might be a normal protective physiological response of the body to slow tumor progression.

Pregnancy has been suggested to be

associated with the suppression of a variety of humeral and cellular mediated immunological functions in order to accommodate the "foreign"semiallogeneic fetal graft.

There is evidence now that immunological recognition of pregnancy is important for the maintenance of gestation, and that inadequate recognition of fetal antigen might result in failed pregnancy[19], i.e. the immunological recognition of the semiallogenic fetus is fallowed by partial alteration in its mechanism to maintain a normal growth and development of the fetus. If this is the case, could immune suppression in cancer patients have a similar function as it is found in pregnancy?

In older patients, beside low immunological vigor, the presence of suboptimal nutrition and concentrations of growth factors may play a role in tumor growth[16,17]. Animal experiments have shown that caloric restriction reduces tumor growth rates but does not improve the prognosis[18]. Growth factors are essential mediators of growth for both normal and tumor cells. In humans, growth factor and nutritional deficiencies may contribute to low tumor progression. This may be true in the elderly in the early stages of tumor development. However, once the tumor reaches the stage of autonomy, it will mobilize the body's stores to increase metabolism. This fact has been attributed to the release of certain polypeptides by tumor cells[16]. Simultaneously, the growth stimulation by growth factors is no longer needed, and the tumor cell will depend on its own intracellular stimulation for growth[17].

In our study, despite the likelihood of lower immunological vigor in the older patients, there was no significant difference in the 5-year survival rates between group I and group II. This may be explained by the fact that we strictly followed the surgical policy described above.

In regard to development of neck metastasis, it would have been an advantage if it had been possible to avoid performing incisional biopsy in all patients in both age groups. However, this was not possible, as some of the tumors did not have the characteristic diagnostic clinical appearance. In addition, some patients were referred to our center after the referring physician had already performed the biopsy. In some patients, biopsy was performed to provide a legal confirmation of our diagnosis to the patient before major surgery.

The following hypotheses could explain the above clinical findings:

In older patients, the decrease in immunity does not present a threat (proliferative stress) to the growing tumor cells, therefore, these will not undergo rapid evolutionary turnover. In addition, the decrease in available growth factors and the poor nutritional status of older patients will not provide the optimal conditions for tumor growth. This quiescent state of the tumor environment may be violated when ineffective chemotherapy or radiotherapy, incomplete surgical resection, or incisional biopsy has been introduced. Autonomy of growth and the ability to metastasize will take place as a result of the emergence of new sublines of tumor cells with better survivability in the new environmental condition. In contrast, in younger patients, their superior immunological status imposes a continuous proliferative stress on tumor cells since the early stages of tumor development, with the subsequent emergence of new subclones of tumor cells having aggressive characteristics.

References

1. Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. *Head Neck Surg* 1988; 10(3):160-167.
2. Feinmesser R, Freeman JL, Noyek AM, Birt BD. Metastatic neck disease. A clinical/radiographic/pathologic correlative study. *Arch Otolaryngol Head Neck Surg* 1987; 113(12):1307-1310.
3. Wensing BM, Vogel WV, Marres HA, Merkx MA, Postema EJ, Oyen WJ, et al. FDG-PET in the clinically negative neck in oral squamous cell carcinoma. *Laryngoscope* 2006;116(5): 809-813. Erratum in: *Laryngoscope* 2006 Jul;116(7 Pt 1):1302.
4. Nahmias C, Carlson ER, Duncan LD, Blodgett TM, Kennedy J, Long MJ, et al. Positron emission tomography/computerized tomography (PET/CT) scanning for preoperative staging of patients with oral/head and neck cancer. *J Oral Maxillofac Surg* 2007 Dec; 65(12): 2524-2535.
5. Colnot DR, Nieuwenhuis EJ, van den Brekel MW, Pijpers R, Brakenhoff RH, Snow GB, et al. Head and neck squamous cell carcinoma: US-guided fine-needle aspiration of sentinel lymph nodes for improved staging-initial experience. *Radiology* 2001;218(1):289-293.
6. DeSanto LW, Beahrs OH. Modified and complete neck dissection in the treatment of squamous cell carcinoma of the head and neck. *Surg Gynecol Obstet* 1988; 167(3): 259-269.
7. Freund H. Robert. Principles of head and neck Surgery. Second Edition p: 59.
8. Medina JE, Byers RM. Supraomohyoid neck dissection: rationale, indications, and surgical technique. *Head Neck* 1989; 11(2):111-122.
9. Colacchio TA, Yeager MP, Hildebrandt LW . Preoperative Immunomodulation in cancer surgery. American journal of surgery. Lebanon, New Hampshire. Jan . 1994, vol.167 No.1:174-179.
10. Stutman O, Immunsupresion and Malignancy. Adv. Cancer Res. 1975,22:261-422
11. Makinodon T. Immunodeficiency and aging. The immune System function and therapy of dysfunction. Edited by G. Gloria and A.Eshkel. p. 56.
12. Scully C. The immunology of cancer of the head and neck with Particular reference to oral cancer. Oral surg Oral Med Oral Pathol 1982;53(2):157-169
13. Vinzenz K, Micksche M. Systemic and regional natural Cytotoxicity in patients with head and neck cancer. J Maxillofac surg 1986;14(5):270-275
14. Sjogren HO, Hellstrom I, Bansal SC, Hellstrom KE. Suggestive evidence that the " blocking antibodies " of tumor-bearing individuals may be antigen-antibody complexes. Proc Natl Acad sci USA 1971:68(6):1372-1375.
15. Schwartz, principle of surgery. 4th edition. P. 326.
16. Solassol CH, H. Joyeux. Ambulatory parental nutrition in Hospital and at home. Inj JE Edit." Total parental nutrition" Boston, 1975.
17. Theologides A. Pathogenesis of cachexia in cancer. A review And hypothesis. Cancer 1972; 29(2):484-488.
18. Tennenbaum A. The genesis and growth of tumors. Cancer Res 1942; 2:460-467.
19. Szekeres-Bartho J., Immunological relationship between the mother and fetus. Int.Rev.Immunol. 2002 Nov-Dec; 2(6): 471-95.